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## Pradofloxacin Oral Suspension, office action, LeA 36165

The following formulations are compared to each other regarding the pharmaceutical quality. Thus, different formulations were manufactured according to the following table 1.

TABLE 1: INGREDIENTS OF THE COMPARED FORMULATIONS.

Ingredients [g / 100 ml]	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Pradofloxacin	2.5	2.5	2.5	2.5
Amberlite IRP 64	10	10	10	10
Sorbic acid	0.2	0.2	0.2	0.2
Ascorbic acid	0.02	0.02	0.02	0.02
Propylene glycol	30	30	30	30
Xanthan	0.7	-	-	-
Silica		0.7	1.5	3.0
Vanilla flavor	0.2	0.2	0.2	0.2
Water, demineralized	ad 100 ml	ad 100 ml	ad 100 ml	ad 100 ml

After manufacturing the formulations were stored at ambient room temperature (about 22 °C). Their viscosity and sedimentation behavior was determined. In table 2 parameters like type of viscosity or the yield point is given and in graph 1 sedimentation behavior can be seen.

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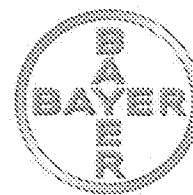


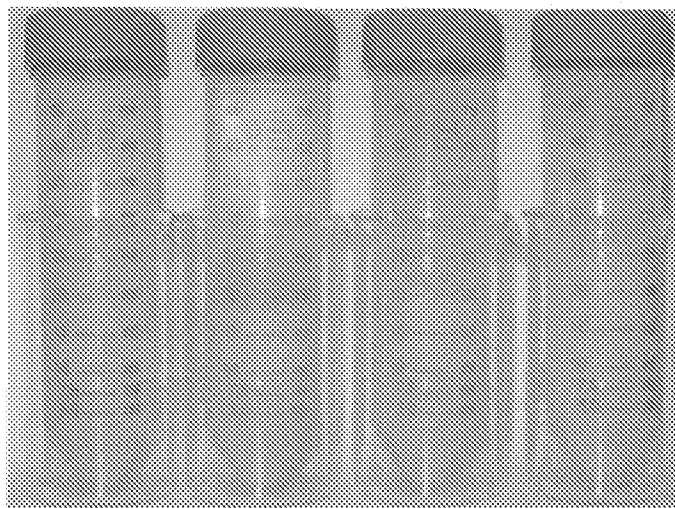
TABLE 2: VISCOSITY PARAMETERS OF THE FORMULATIONS.

Ingredients [g / 100 ml]	Form. 1	Form. 2	Form. 3	Form. 4
Xanthan	0.7	-	-	-
Silica		0.7	1.5	3.0
viscosity type	thixotropic	not thixotropic	not thixotropic	not thixotropic
yield point (tau)	13.6 Pa	0.6 Pa	0.5 Pa	1.5 Pa

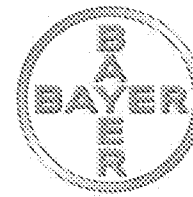
The formulation with Xanthan is thixotropic and has a yield point of about 13.6 Pa. All formulations with Silica are not thixotropic and they hardly have any yield point.

A thixotropic system with a yield point is advantageous because phase separation or sedimentation is avoided below that yield point. This makes it easier to transport and store the formulations. Upon shaking the yield point is overruled and the system is as liquid as formulations without any yield point which makes them easy to administer.

Sedimentation behavior is easy to assess by the following picture (graph 1). It shows the stored formulations after 72 hours.



Graph 1: sedimentation behavior after 72 h at room temperature for the formulations with 0.7 % Xanthan, 0.7 % Silica, 1.5 % Silica, 3.0 % Silica



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The formulation containing Xanthan (0.7 %) shows no sedimentation at all. All formulations containing Silica show significant sedimentation!

With 0.7 % Silica the strongest sedimentation occurs, with 1.5 % Silica the sedimentation is only slightly less and with 3.0 % Silica sedimentation is less but still half of the complete formulation -about 50 % sedimentation!

Formulation showing quick and severe sedimentation - like the ones with Silica- are difficult to dose accurately and they always bear the risk of not being homogenized sufficiently upon shaking. This is especially for elderly persons the case. Sometimes it is even impossible to redispers sedimented suspensions due to a clogging of the dispersed particles ("caking").

A formulation with Xanthan has important advantages regarding the pharmaceutical quality due to the viscosity and the resulting sedimentation behavior.

Kind regards,

(Dr. Iris Heep)

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